REMARKS

The Advisory Action mailed October 22, 2002 has been received and reviewed. Claims 1, 2, 4-14, 16-21, 24-26, 28-32 and 37-58 are pending in the application. All claims stand rejected. Applicants propose to amend claims 2, 19, 21, 25, 37, 38-40, 42 and 44-57 and add new claim 59 as set forth herein. Claims 1, 4-18, 20, 24, 26, 41 and 43 are to be cancelled. All amendments and cancellations are made without prejudice or disclaimer. Reconsideration is respectfully requested.

I. Double Patenting

The Final Office Action indicated that if claim 5 were found allowable, claims 6-8 and 41 would have been objected to under 37 C.F.R. § 1.75 as being substantial duplicates thereof. Claims 5, 6-8 and 41 have been cancelled rendering the double patenting objections moot.

II. Claim Objections

Claim 10 was objected to under 37 C.F.R. § 1.75(c) as being of improper dependent format. Claim 10 has been cancelled rendering the objection moot.

III. 35 U.S.C. § 112, Second Paragraph

Claims 2, 25, 37-40 and 42

Claims 2, 25, 37-40 and 42 stand rejected under 35 U.S.C. § 112, second paragraph, as assertedly being indefinite for failing to particularly point and distinctly claim the subject matter which applicants regard as the invention. Applicants propose to amend claims 2, 38-40 and 42, and partially in view of the amendments respectfully request the rejections be withdrawn.

Independent claim 2 and claims 37-40 and 42 depending therefrom, as proposed to be amended, are directed to a recombinant adenovirus with a reduced tissue tropism for liver cells, and independent claim 25 is directed to an adenovirus capsid with a reduced tissue tropism for liver cells. Although applicants do not agree with the statement in the Final Office Action that it is unclear as to what extent the reduced tissue tropism between wild type adenovirus 5 and chimeric adenovirus for liver cells is "significant," for the sake of expedited prosecution,

applicants propose to remove the term "significantly" from the claims.

As amended, claims 2 and claims 37-40 and 42 are directed to a reduced tissue tropism. The claims are supported by Table II, which compares the results for lung and kidney cells, not just liver cells. Table II on page 47 of the specification indicates the difference in luciferase activity between samples from liver cells when the control Ad5 is used and when the recombinant adenoviruses of the present invention are used. As illustrated on the top line of Table II, which corresponds to data for liver cells, the counts decrease from 740045 in control Ad5 adenovirus to reduced counts of 458, 8844, 419 and 2033 in recombinant adenoviruses Fib 12, Fib 16, Fib 28 and Fib 40-L, respectively. The counts for the recombinant adenoviruses are reduced by at least 1000 fold when liver cells are compared, thus supporting the phrase "reduced tissue tropism for liver cells."

Accordingly, reconsideration and withdrawal of the rejections of claims 2, 25, 37-40 and 42 are requested.

Claim 37

Claim 37 stands rejected under 35 U.S.C. § 112, second paragraph, as being assertedly incomplete for omitting essential steps, resulting in a gap between the steps. Applicants propose to amend to claim 37 as set forth herein, and in view of the amendment respectfully traverse the rejection.

Applicants propose to amend claim 37 to include additional steps in the method. In view of the proposed amendment to claim 37 and the data supporting the reduced tissue tropism of the adenovirus capsid, reconsideration and withdrawal of the rejection of claim 37 is requested.

Claim 10

Claim 10 stands rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Claim 10 has been cancelled rendering the rejection moot.

IV. 35 U.S.C. § 112, First Paragraph

Claims 2, 38-40, 44, 45, 51, 52 and 54-57

Claims 2, 38-40, 44, 45, 51, 52 and 54-57 stand rejected under 35 U.S.C. § 112, first paragraph, as assertedly containing subject matter which was not described in the specification in such a way to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention. Applicants propose to amend claims 2, 38-40, 44, 45, 51, 52 and 54-57, and in view of the amendments respectfully traverse the rejections.

Specifically, it was thought that the scope of the claimed invention was very broad and that the few examples provided in the specification were not sufficient to represent the full scope of the claimed invention. The proposed amendments replace the phrase "gene delivery vehicle" with the phrase "recombinant adenovirus." Since the specification provides support for the recombinant adenovirus with reduced tissue tropism for liver cells as recited in claims 2 and 38-40 (*e.g.*, Table II, top line) and the recombinant adenovirus with an increased tissue tropism for endothelial cells as recited in claims 44, 45, 51, 52 and 54-57 (*e.g.*, Figure 7A), reconsideration and withdrawal of the rejections are requested.

Claims 1, 2, 4-14, 16-21, 24-26, 28-32 and 37-58

Claims 1, 2, 4-14, 16-21, 24-26, 28-32 and 37-58 stand rejected under 35 U.S.C. § 112, first paragraph, because the specification assertedly does not reasonably provide enablement for any gene delivery vehicle comprising at least a tissue tropism for smooth muscle cells, increased tropism for endothelial cells, or with a significantly reduced tissue tropism for liver cells for *in vitro* or *in vivo* gene delivery. Applicants have cancelled claims 1, 4-14, 16-18, 20, 24, 26, 41 and 43 rendering the rejection of these claims moot, propose to amend claims 2, 19, 38-40, 42, and 44-57, and in view of the proposed amendments respectfully traverse the rejections.

As proposed to be amended, claims 2, 38-40, 42 and 44-57 are directed to recombinant adenoviruses and not to any gene delivery vehicle. Since the application provides support for a cell that produces a recombinant adenovirus with a tropism for smooth muscle cells as recited in claim 19, a recombinant adenovirus with an increased tropism for endothelial cells when compared to wild-type virus as recited in claims 44-57, an adenovirus capsid having an increased

tissue tropism for endothelial cells as recited in claim 58, an adenovirus capsid with a reduced tissue tropism for liver cells as recited in claim 25, a method of reducing a tissue tropism of an adenovirus capsid for liver cells as recited in claim 37, and a recombinant adenovirus with a reduced tissue tropism for liver cells as recited in claims 2, 38-40 and 42, the claims are enabled. Accordingly, reconsideration and withdrawal of the rejections are requested.

Claim 10

Claim 10 also stands rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which assertedly was not described in the specification in such a way to reasonably convey to one skilled in the relevant art that the inventors has possession of the claimed invention. Claim 10 has been cancelled rendering the rejection moot.

V. 35 U.S.C. § 102(b)

Claims 1, 4-8, 11-14, 16, 17, 19, 24 and 41

Claims 1, 4-8, 11-14, 16, 17, 19, 24 and 41 stand rejected under 35 U.S.C. § 102(b) as assertedly being anticipated by Stevenson et al. Claims 1, 4-8, 11-14, 16, 17, 24 and 41 have been cancelled rendering the rejections of these claims moot. Applicants propose to amend claim 19 to include the subject matter of claim 20, which was not rejected as being anticipated. Withdrawal of the anticipation rejection of claim 19 is thus requested.

Claims 1, 4-8, 10-14, 16, 17, 19, 24 and 41

Claims 1, 4-8, 10-14, 16, 17, 19, 24 and 41 stand rejected under 35 U.S.C. § 102(b) as assertedly being anticipated by Wickham et al. Claims 1, 4-8, 10-14, 16, 17, 24 and 41 have been cancelled rendering the rejections of these claims moot. Applicants propose to amend claim 19 to include the limitations of claim 20, which was deemed not anticipated by Wickham et al. Accordingly, withdrawal of the anticipation rejection of claim 19 is requested.

VI. 35 U.S.C. § 103(a)

Claims 1, 4-14, 17-19, 24, 26 and 43

Claims 1, 4-14, 17-19, 24, 26 and 43 stand rejected under 35 U.S.C. § 103(a) as assertedly being unpatentable over Wickham et al. in view of Stevenson et al. and Woo et al. Claims 1, 4-14, 17, 18, 24, 26 and 43 have been cancelled rendering the rejections of these claims moot. Further, Applicants propose to amend claim 19 to include the limitations of claim 20, which was not rejected as being obvious. In view of the proposed amendment of claim 19 to include the subject matter of claim 20, withdrawal of the obviousness rejection of claim 19 is requested.

VII. Lack of Antecedent Basis

The Advisory Action indicated that claim 21 lacked antecedent basis as depending from canceled claim 1. Applicants propose to amend claim 21 to depend from claim 2. In view of the proposed amendment, antecedent basis should be present.

VIII. Budapest Declaration

Attached hereto is a Declaration Under 37 C.F.R. §§ 1.801-1.809 signed by Dr. Jaap Goudsmit indicating that the cell line PER.C6 has been deposited under number ECACC 96022940 as well as copies of deposit certificates indicating such deposit. Accordingly, the requirements of 35 U.S.C. § 112 should be satisfied regarding claim 19 which claims the referenced cell line.

ENTRY OF AMENDMENTS

The proposed amendments to the claims should be entered because they are supported by the as-filed specification and drawings and do not add any new matter to the specification. Further, the amendments should not raise new issues or require a further search. Since the

amendments comply with requirements to form set forth in the Final Office Action and the Advisory Action, and further place the application in condition for allowance, the amendments should be entered. If the amendments do not place the application in condition for allowance, entry is respectfully requested since they certainly remove issues for appeal.

CONCLUSION

In view of the proposed amendments and remarks presented herein, applicants respectfully submit that the amended claims define patentable subject matter. If questions remain after consideration of the foregoing, the Examiner is kindly requested to contact applicants' attorney at the address or telephone number given herein.

Respectfully submitted,

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Date: October 29, 2002
AFN/afn
Document in ProLaw

VERSION WITH MARKINGS TO SHOWN CHANGES MADE

2. (Thrice amended) A [gene delivery vehicle] recombinant adenovirus with a [significantly] reduced tissue tropism for liver cells.

19. (Four times amended) A cell for producing a [gene delivery vehicle] recombinant adenovirus having a tissue tropism for smooth muscle cells, said cell comprising:
means for the assembly of [gene delivery vectors] said recombinant adenovirus wherein said means includes at least one adenovirus nucleic acid for the production of an adenoviral fiber protein, wherein said adenoviral fiber protein comprises at least a tissue tropism determining fragment of a subgroup B adenoviral fiber protein and wherein said cell is of PER.C6 (ECACC deposit number 96022940) origin.

21. (Twice amended) A pharmaceutical composition comprising the [gene delivery vehicle] recombinant adenovirus of claim [1] 2 together with a suitable vehicle.

25. (Four times amended) An adenovirus capsid with a [significantly] reduced tissue tropism for liver cells wherein said adenovirus capsid comprises proteins from at least two different adenoviruses and wherein at least a tissue tropism determining fragment of a fiber protein is of subgroup B adenovirus origin.

37. (Four times amended) A method of reducing [an adenovirus capsid of] a tissue tropism of an adenovirus capsid for liver cells, said method comprising: [incorporating a fragment of a fiber protein of adenovirus 16 in an adenovirus capsid therefor.]

i) exchanging a first nucleic acid encoding the tissue-tropism determining fragment of a fiber protein for a second nucleic acid encoding the tissue-tropism determining fragment of a fiber protein of adenovirus 16;

ii) introducing the resulting nucleic acid from step i) into a cell capable of producing said adenovirus capsid; and

iii) allowing said cell to produce said adenovirus capsid in a suitable medium.

38. (Amended) The [gene delivery vehicle] recombinant adenovirus of claim 2 wherein said tissue tropism is [being] provided by a virus capsid.

39. (Amended) The [gene delivery vehicle] recombinant adenovirus of claim 38, wherein said virus capsid comprises protein fragments from at least two different viruses.

40. (Amended) The [gene delivery vehicle] recombinant adenovirus of claim 39, wherein at least one of said viruses is an adenovirus.

42. (Twice Amended) The [gene delivery vehicle] recombinant adenovirus of claim 40 wherein at least one of said protein fragments comprises a tissue tropism determining fragment of a fiber protein from a subgroup B adenovirus.

44. (Twice Amended) A [gene delivery vehicle] recombinant adenovirus comprising increased tissue tropism for endothelial cells when compared to other [gene delivery vehicles] recombinant adenovirus, wherein said tissue tropism is [being] provided by a virus capsid and wherein said virus capsid comprises protein fragments from at least two different viruses.

45. (Amended) The [gene delivery vehicle] recombinant adenovirus of claim 44 wherein at least one of said viruses is an adenovirus.

46. (Amended) The [gene delivery vehicle] recombinant adenovirus of claim [44] 45 wherein at least one of said viruses is a subgroup B adenovirus.

47. (Twice Amended) The [gene delivery vehicle] recombinant adenovirus of claim 44 wherein at least one of said protein fragments comprises a tissue tropism determining fragment of a fiber protein of subgroup B adenovirus origin.

48. (Amended) The [gene delivery vehicle] recombinant adenovirus of claim [44] 46 wherein said subgroup B adenovirus is adenovirus 16.

49. (Twice Amended) The [gene delivery vehicle] recombinant adenovirus of claim 44 wherein said protein fragments are [not from an adenovirus of subgroup B and are] of adenovirus [of] subgroup C origin.

50. (Amended) The [gene delivery vehicle] recombinant adenovirus of claim 44 wherein said virus capsid comprises protein fragments from at least two different viruses and wherein said protein fragments are [not from an adenovirus of subgroup B and are] from an adenovirus of subgroup C.

51. (Amended) The [gene delivery vehicle] recombinant adenovirus of claim 44 [wherein] further comprising an adenoviral nucleic acid.

52. (Twice Amended) The [gene delivery vehicle] recombinant adenovirus of claim 51 wherein said adenoviral nucleic acid comprises sequences from at least two different adenoviruses.

53. (Amended) The [gene delivery vehicle] recombinant adenovirus of claim 51 wherein said adenoviral nucleic acid comprises at least one sequence encoding a fiber protein comprising a tissue tropism determining fragment of a subgroup B adenovirus fiber protein.

54. (Amended) The [gene delivery vehicle] recombinant adenovirus of claim 51 wherein said adenoviral nucleic acid is modified such that the capacity of said adenoviral nucleic acid to replicate in a target cell has been reduced or disabled.

55. (Amended) The [gene delivery vehicle] recombinant adenovirus of claim 44, [further comprising] wherein said recombinant adenovirus comprises a minimal adenovirus vector or an Ad/AAV chimaeric vector.

56. (Amended) The [gene delivery vehicle] recombinant adenovirus of claim 44 further comprising at least one non-adenoviral nucleic acid.

57. (Amended) The [gene delivery vehicle] recombinant adenovirus of claim 56 wherein at least one of said non-adenoviral nucleic acids is a gene selected from the group of genes encoding a protein selected from the group consisting of: an apolipoprotein, a nitric oxide synthase, a herpes simplex virus thymidine kinase, an interleukin-3, an interleukin-1α, an [(anti)] angiogenesis protein, an anti-angiogenesis protein, an anti-proliferation protein, a smooth muscle cell anti-migration protein, a vascular endothelial growth factor [(VGEF)], a basic fibroblast growth factor, a hypoxia inducible factor 1α [(HIF-1α)] and a PAI-1.

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Vogels et al.

Serial No.: 09/444,284

Filed: November 19, 1999

For: GENE DELIVERY VECTORS PROVIDED WITH A TISSUE TROPISM FOR SMOOTH MUSCLE CELLS, AND/OR ENDOTHELIAL CELLS

Confirmation No.: 8464

Examiner: S. Chen, Ph.D.

Group Art Unit: 1632

Attorney Docket No.: 2183-4231US

NOTICE OF EXPRESS MAILING

Express Mail Mailing Label Number: EV058347085US

Date of Deposit with USPS: October 29, 2002

Person making Deposit: Jon Wentz

Declaration Under 37 C.F.R. §§ 1.801-1.809

Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Dr. Jaap Goudsmit, hereby certify that I am the Chief Scientific Officer of Crucell Holland B.V., successor in interest of INTROGENE B.V. ("Introgene"), and declare that:

1. I am formed and believe that Introgene is the assignee of U.S. Patent Application serial no. 09/444,284.

2. A am informed and believe that on February 29, 1996, Introgene made a deposit of cell line PER.C6 under number ECACC 96022940 under the provisions of the Budapest Treaty with the Centre for Applied Microbiology and Research Authority (European Collection of Animal

Cell Cultures), Porton Down, Salisbury, Wiltshire SP4, OJG, United Kingdom, an International Depository Authority, in accordance with the Budapest Treaty.

3. On behalf of Introgene, I state that all restrictions upon public access to the deposit (except those permitted by 37 C.F.R. § 1.808(b)) will be irrevocably removed upon the grant of a U.S. Patent on this U.S. Patent application, and the deposit will be replaced if viable samples cannot be dispensed by the depository.

4. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the U.S. Code and that such willful false statements may jeopardize the validity of the patent.

Date: 1 Oct 2002

Jaap Goudsmit

Dr. Jaap Goudsmit

Document in ProLaw

ecacc
European Collection of Cell Cultures

Centre for Applied Microbiology and Research
&
European Collection of Cell Cultures

This document certifies that Cell Culture
(Deposit Ref. 96022940) has been accepted as a patent deposit,
in accordance with
The Budapest Treaty of 1977,
with the European Collection of Cell Cultures on 29TH February 1996

P J Packer

Dr P J Packer
Quality Manager, ECACC

CAMR
Today's Research
European Collection of Cell Cultures, CAMR, Salisbury, Wiltshire SP4 0JG UK.
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BUDAPEST TREATY ON THE INTERNATIONAL
RECOGNITION OF THE DEPOSIT OF MICROORGANISMS
FOR THE PURPOSES OF PATENT PROCEDURE

INTERNATIONAL FORM

TO

CRUCELL HOLLAND B.V.
ARCHIMEDESWEG 4
PO BOX 2048
2301 CA LEIDEN
THE NETHERLANDS

NAME AND ADDRESS
OF DEPOSITOR

I. IDENTIFICATION OF THE MICROORGANISM

Identification reference given by the DEPOSITOR:
PER C6

Accession number given by the INTERNATIONAL DEPOSITARY AUTHORITY:
96022940

II. SCIENTIFIC DESCRIPTION AND/OR PROPOSED TAXONOMIC DESIGNATION

The microorganism identified under I above was accompanied by:

[X] A scientific description

[ ] A proposed taxonomic designation

(Mark with a cross where applicable)

III. RECEIPT AND ACCEPTANCE

This International Depository Authority accepts the microorganism identified under I above, which was received by it on 29th February 1996 (date of the original deposit)[1]

IV. RECEIPT OF REQUEST FOR CONVERSION

The microorganism identified under I above was received by this International Depository Authority on (date of the original deposit) and
A request to convert the original deposit to a deposit under the Budapest Treaty was received by it on (date of receipt of request for conversion)

IV. INTERNATIONAL DEPOSITORY AUTHORITY

Name: Dr P J Packer

Address: ECACC
CAMR
Porton Down
Salisbury SP4 OJG

Signature(s) of person(s) having the power to represent the International Depository Authority or of authorized officials(s):

Date: 26/2/01 PJ Packer

1 Where Rule 6.4(d) applies, such date is the date on which the status of international depositary authority was acquired

BUDAPEST TREATY ON THE INTERNATIONAL
RECOGNITION OF THE DEPOSIT OF MICROORGANISMS
FOR THE PURPOSES OF PATENT PROCEDURE

INTERNATIONAL FORM

TO

CRUCELL HOLLAND B.V.
ARCHIMEDESWEG 4
PO BOX 2048
2301 CA LEIDEN
THE NETHERLANDS

VIABILITY STATEMENT
Issued pursant to Rule 10.2 by the
INTERNATIONAL DEPOSITARY AUTHORITY
identified on the following page

NAME AND ADDRESS OF THE PARTY
TO WHOM THE VIABILITY OF STATEMENT
IS ISSUED

I. DEPOSITOR	II. IDENTIFICATION OF THE MICROORGANISM
Name: CRUCELL HOLLAND B.V. Address: ARCHIMEDESWEG 4 PO BOX 2048 2301 CA LEIDEN THE NETHERLANDS	Accession number given by the INTERNATIONAL DEPOSITORY AUTHORITY: 96022940 Date of the deposit or of the transfer: 29th February 1996

II. VIABILITY STATEMENT

The viability of the microorganism identified under II above was tested on [2]. On that date, the said microorganism was

[X] [3] viable

[ ] [3] no longer viable

1 Indicate the date of the original deposit or, where a new deposit or a transfer has been made, the most relevant date (date of the new deposit or date of the transfer).

2 In the cases referred to in Rule 10.2 (a) (ii) and (iii), refer to the most recent viability test.

3 Mark with a cross the applicable box.

IV. CONDITIONS UNDER WHICH THE VIABILITY TEST HAS BEEN PERFORMED [4]	
V. INTERNATIONAL DEPOSITARY AUTHORITY	
Name: Dr P J Packer ECACC CAMR Address: Porton Down Salisbury Wiltshire SP4 0JG	Signature(s) of person(s) having the power to represent the International Depositary Authority or of authorized official(s): Date: 26/2/01 PSlade

4 Fill in if the information has been requested and if the results of the test were negative.